REMARKS

The Amendment, filed in response to the Office Action mailed August 19, 2008, is believed to fully address all and every issue raised in the Action. A favorable reconsideration of the application is respectfully requested.

Claims Disposition

Claims 1-4 are all the claims pending in the application. Claims 1-4 are considered and rejected in the Action.

Upon entry of the amendment, which is respectfully requested, claim 1 will be amended to more clearly point out the feature of the claimed subject matter as well as remove informality. Amendment to claim 1, in particular, the limitation "wherein 40% or more of metformin is released within 2 hours after the formulation is immersed in a gastric fluid" is supported by the disclosure at pages 12-13, which explains the formulation and its release rate test methods and results, and Figures 1-6. Thus, no new matter is introduced.

Drawings

Applicants note that the Office does not indicate whether or not the drawings filed September 29, 2006 are accepted or not. From the fact that the drawings are not objected, applicants assume that the drawings are accepted. The Examiner is respectfully requested to check the box 10).a) on Office Action Summary.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing previous rejection under 35 U.S.C. § 103 over Sanghvi in view of Shell based on the applicants' arguments and/or amendments.

Response to the Rejection under 35 U.S.C. § 112, Second Paragraph

In the Action, claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office asserts that the term "pharmaceutically acceptable additive" is indefinite as it unclear what is encompassed by the term, because there is no definition stating that the term "pharmaceutically acceptable additive" is meant to excipients, even though the specification provides examples such as diluents and lubricants.

Also, the Office points out the term "weight ratio" is indefinite as it unclear what is encompassed by the term because it is unclear if the ratio is the weight of the materials (e.g. grams) or the weight percentage of the components in the composition.

Without acquiescing the rejection, claim 1 is amended to replace the term "pharmaceutically acceptable additive" to "pharmaceutically acceptable excipient." As the Office correctly notes, the specification of the instant application, at page 4, provides a description that the formulation of the subject invention can contain pharmaceutical additives such as neutralized diluents carriers, binders and lubricants, and the additives are conventional additives in the pharmaceutical field used in solid formulations for oral administration. Accordingly, it is easily recognized to a person skilled in the art that the pharmaceutical additive is not an active compound or drug, but an inactive compound used as a diluents or vehicle for drug, etc., i.e., an excipient.

Also, in response to the rejection of the term "weight ratio," in order to clarify that the ratio is the weight ratio of the components in the composition, the symbol ":" is replaced with

"to." The amended claim 1 clearly sets forth the ratios of the weights of the components of the claimed formulation.

Therefore, it is believed that the rejections of claims 1 to 4 under 35 U.S.C. § 112 have been moot by the amendments, and their withdrawal is respectfully requested.

Response to Rejection under 35 U.S.C. § 103(a)

In the Action, claims 1-4 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Berner et al. (U.S. Pat. Publication 2003/0104062) ("Berner").

The Office asserts that Berner teaches a pharmaceutical control release dosage form for drugs, preferably high solubility drugs including and exemplifying metformin hydrochloride, wherein the composition comprises water-swellable polymers in the core and shell to achieve appropriate control release. Berner is further relied upon to teach that suitable polymers include polyalkylene oxides, xanthan gum, and polysaccharide gums (i.e. natural gums, e.g. xanthan), that the preferred range of the viscosity-average molecular weight ratio of core: shell is about 0.2:1 to about 1:1.

The Office admits that Berner does not expressly teach an example with a natural gum such as xanthan gum in a metformin composition with polyethylene oxide.

However, the Office asserts that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute xanthan gum or other natural polysaccharide gums for polyethylene oxide in the core or the shell in Example 1, as suggested by Berner, and produce the instant invention; and that it would have been obvious to substitute one material for another depending on the desired appropriate control release, availability, and properties for the final product. In addition, the Office contends that one of ordinary skill in the art would have been motivated to do this because it is desirable for manufacturers to have

analogous choices to substitute the water-swellable polymers in the core and shell to achieve appropriate control release when motivated by pricing, availability, or desired properties of the final product.

Applicants respectfully traverse for the following reasons.

1) The Claimed Formulation

The subject invention defined in claims 1-4 relates to a controlled release formulation for oral administration of metformin comprising a mixture of a polyethylene oxide and a natural gum as a carrier and having specific weight ratios between metformin and carrier, and polyethylene oxide and natural gum, thereby exhibiting 40% or more of releasing rate within 2 hours after the formulation is immersed in a gastric fluid.

Also, as discussed and shown in detail in the previous Amendments and Rule 1.132 Declaration, filed June 13, 2008, the claimed formulation, which has the components and mixing ratios as defined in claim 1, shows a release profile of metformin that more than 40% or more of metformin is released within 2 hours after the formulation is immersed in a gastric fluid and it takes 9 hours or more to release 90% of the metformin from the formulation. See Figures 1-6 of the application and Ruel 1.132 Declaration filed June 13, 2008.

That is, the specific releasing profile of metformin over a period of time can be only achieved by using the specific mixture (not having a core-shell structure) and specific weight ratios of the components.

2) Teaching of Berner Reference

Berner teaches a shell-and core dosage form approaching zero-order drug release comprising water-swellable polymers such as polyalkylene oxides, xanthan gum, or

polysaccharide gums. Further, in Berner, a preferred polyalkylene oxide is polyethylene oxide having about 4,000,000 to about 8,000,000 of molecular weight.

However, Berner teaches or suggests neither a combination of polyethylene oxide and natural gum, nor specific weight ratios between metformin and carrier, and polyethylene oxide and natural gum. Moreover, Berner requires a core-shell structure as an essential element of the formulation to obtain zero-order kinetics (see paragraph [0006]).

3) Comparison of the Claimed Formulation with Berner Reference

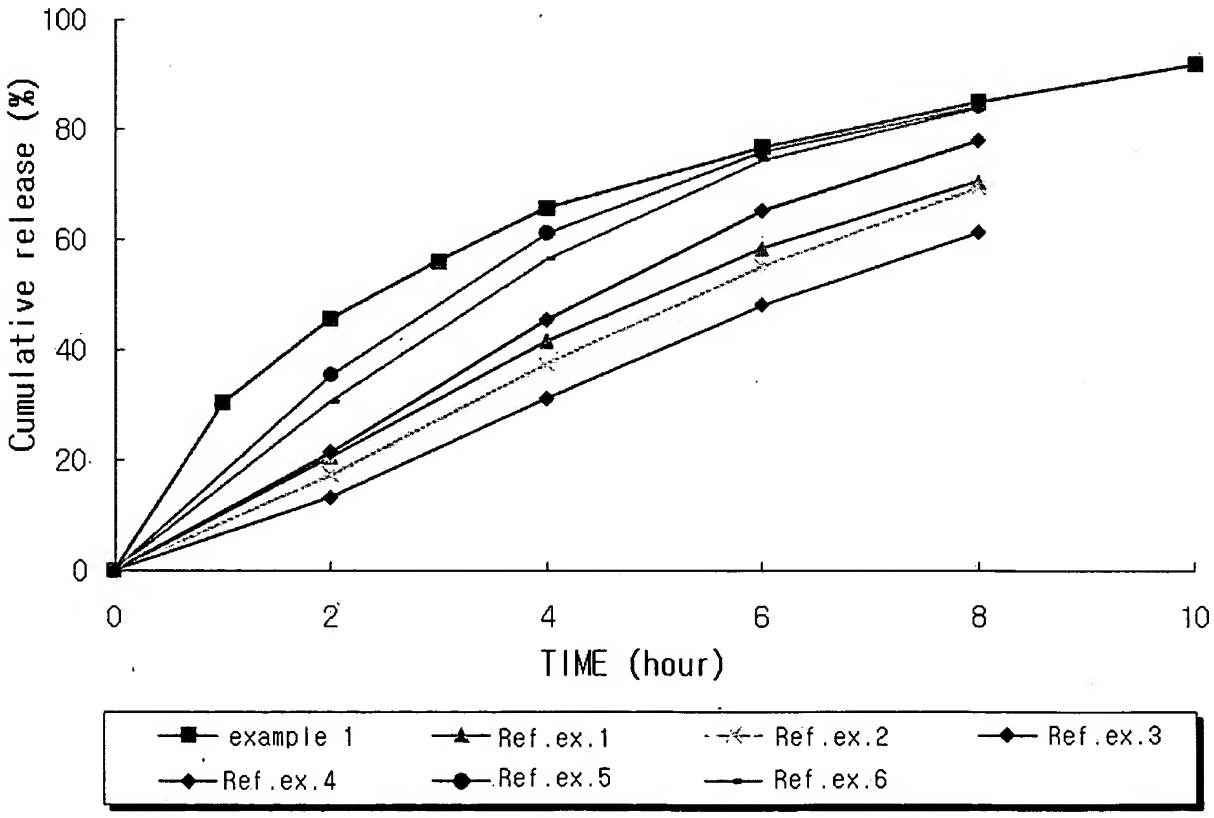
As can be seen the above, Berner teaches that it is well known in the art that a nearly constant release rate that stimulates zero order kinetics can be obtained by a core-shell structure. Further, although Berner discloses that different polymers may be employed in the core and shell, it fails to teach or suggest that a mixed polymer can be contained in either the core or shell. Accordingly, the person skilled in the art would recognize that a tablet should have a core-shell structure employing only one kind of polymer in the core and shell, respectively, in order to have constant release and zero order kinetics.

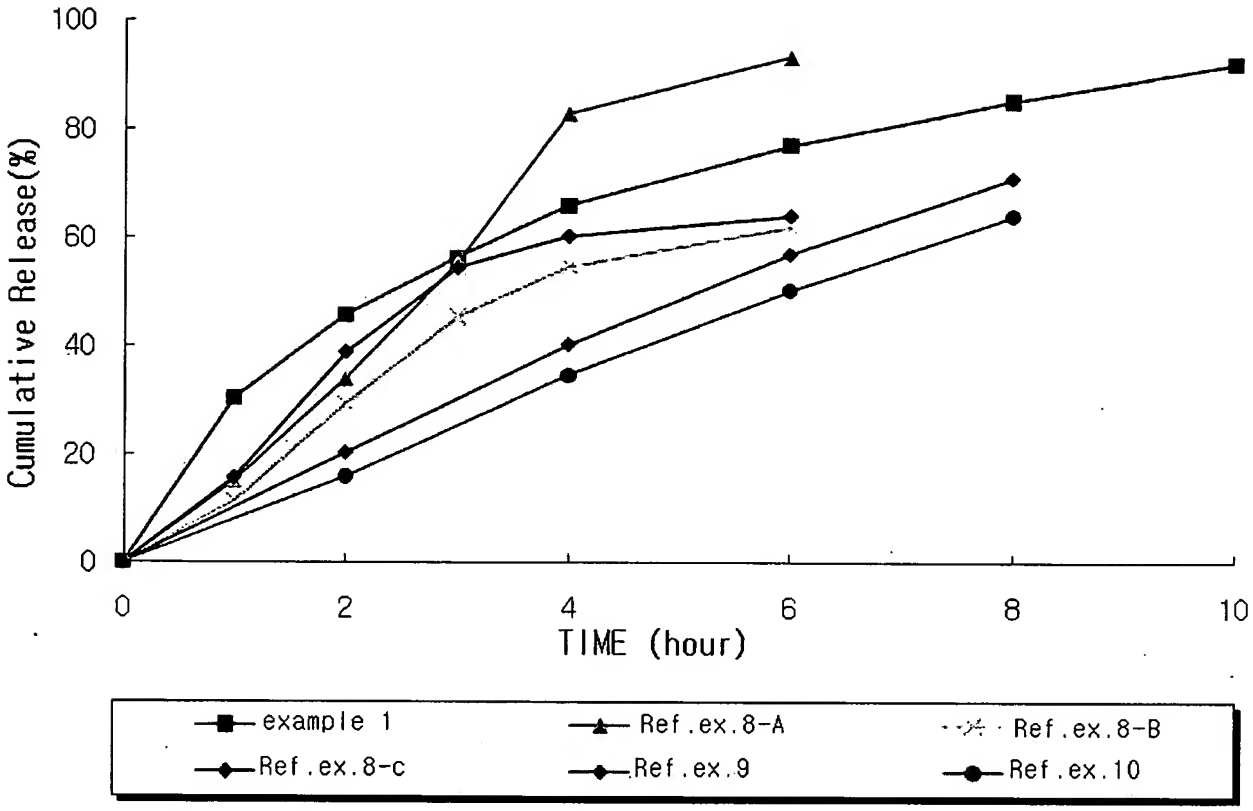
Therefore, contrary to the Office's contention that one of ordinary skill in the art would have been motivated to do this because it is desirable for manufacturers to have analogous choices to substitute the water-swellable polymers in the core and shell to achieve appropriate control release when motivated by pricing, availability, or desired properties of the final product, one of ordinary skill would not have been motivated to use a mixture of polyethylene oxide and a natural gum, as required in claim 1.

Although the Office asserts that Berner discloses a polysaccharide gum such as xanthan gum as an example of suitable polymers, any combination of any polyethylene oxide and any polysaccharide gums are not taught in Berner.

Moreover, Berner fails to teach the specific weight ratios between metformin and carrier, and polyethylene oxide and natural gum. Applicants further respectfully submit that Berner also fails to provide one of ordinary skill in the art with a motivation to modify its teachings to reach the currently claimed subject matter, because Berner requires the essential "core and shell" structure, rather than a mixture of polyethylene oxide and a natural gum in a certain ratio.

The following shows in more detail that the claimed formulation exhibits 40% or more releasing rate of metformin within 2 hours after immersion in artificial gastric fluid as shown in Figures 1 to 4 of the subject application. Comparison of releasing rates of the claimed formulation with that disclosed in Examples of Berner (see Tables 1 to 10) is shown below.





("Ref. ex." refers to an example of Berner)

As shown in the above, the Figures of Berner exhibit the releasing rates below 40% within 2 hours after immersion in a gastric fluid, while all releasing rates of the claimed formulation are 40% or more. Moreover, considering conditions of release tests, said releasing rates of Berner would be much lower than 40% since the rpm of a paddle in Berner is 60, which is much faster than that of the claimed formulation, i.e., 50 rpm.

It is well known to a person skilled in the art that the releasing effective amount of a drug at the initial state is important in designing a controlled release drug formulation, as well as zero-

order kinetics and constant release, because the term "controlled release" means constant, prolonged and "effective" release of a drug in the related art.

In this regard, such a low releasing rate at the initial state, i.e., within 2 hours after immersion in a gastric fluid, cannot be effective for the treatment of diabetes.

However, the subject invention exhibits properly effective releasing profile of metformin as well as zero order kinetics and constant release by the specific combination of technical constituents, i.e., a mixture of a polyethylene oxide and a natural gum as a carrier together with specific weight ratios between metformin and carrier, and polyethylene oxide and natural gum.

Accordingly, it is believed that the rejection is not sustainable and its withdrawal is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number **202-775-7588**.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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